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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,155	03/01/2004	Arnon Lavie	02-134-D	3822

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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,155	LAVIE ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments and Amendment

The Amendment filed on 10/19/06 in response to the previous Non-Final Office Action (7/19/06) is acknowledged and has been entered.

Claims 2-5, 9-68, and 70-169 have been cancelled previously. Claims 1, 6-8 and 69 are pending and under consideration.

The following office action contains NEW GROUNDS of rejection.

Rejections Withdrawn

The rejection of claims 1, 6,8, and 69 under *35 USC § 112 1st written description* is withdrawn in view of the applicant's argument.

The following is a New Ground of rejection-based on new consideration

Rejection under 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 6-8, and 69 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

Claims are drawn to an antibody-conjugated enzyme, wherein the enzyme is modified deoxycytidine kinase (dCK) having an amino acid sequence of SEQ ID NO: 5 and antibody is CD33 antibody comprising HuM195.

The specification on page 11-13 teaches AraC, as nucleoside analog prodrug, is a most active agent in treating acute myeloid leukemia (AML, page 13) and teaches modified dCK (SEQ ID NO: 5) having enhanced kinase activity of dCK to phosphorylate nucleoside analog, to increase the efficacy of the analogs, such as AraC. The specification then teaches that a conjugate of modified dCK and antibody to CD33 specifically binds to the protein primarily expressed in AML cells and is internalized into

the cells. The specification further teaches that Arac is administered to a patient with antibody-enzyme conjugate, which increases the concentration of nucleoside analogue NA-triphosphate in the targeted cell and results in increased cytotoxicity in the cells. Although the specification particularly teaches that the conjugate specifically recognizes the antigen on the tumor cell and is internalize into the cell, the specification does not teach whether or how the dCK conjugate penetrates the membrane into the nucleus to phosphorylate the nucleoside analog because the process seem to occur inside the nucleus, not in the cytoplasm of the cells.

The instant claims are drawn to an antibody-conjugated modified dCK of SEQ ID NO:5. In order to fulfill the requirements of 35 U.S.C. 101, said conjugate must be indicative of a specific, substantial and credible utility, such as the utility for treating cancer. Although the specification assert that the conjugate is used for treating leukemia, the disclosure does not teach whether or how the conjugate work in order to achieve the purpose. The specification does not provide enough convinced evidence to support the claimed conjugate work more effective when the cells were treated with AraC with the conjugate compared to without the conjugate (see fig 9).

A substantial utility, *by definition*, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In the instant case, antibody-conjugated modified dCK of SEQ ID NO: 5 suggests a potential for treatment purpose, which, at the most, is an interesting invitation for further research and confirmation as it is not a practical method for "real world" use, and it requires significant further research and experimentation in order to form a useful and practical treatment method, which, by no means, is a routine or conventional experimentation. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the claimed invention is not considered substantial. As discussed above, the specification does not provide enough convinced evidence or guidance to support that the claimed conjugate could work or effectively work to kill the cancer cells when the conjugate is internalized into cytoplasm, not into the nucleus of the cell.

Therefore, without objective evidence indicating how to use the antibody conjugated dCK (SEQ ID NO: 5) in treating leukemia blast cells, the instant claims lack a specific, substantial, and credible asserted utility.

Claims 1, 6-8 and 69 are also rejected under 35 U.S.C. 112, first paragraph as below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-8 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are indefinite because the term "an amino acid sequence....SEQ ID NO: 5" in claim 1 is not clear. It cannot be determined whether "an amino acid sequence" means the amino acid sequence of SEQ ID NO: 5 or any fragment of SEQ ID NO: 5 because the claim language "an amino acid sequence" reads on any fragment of or as small as two amino acid peptide fragment of SEQ ID NO: 5. Claim 1 renders the dependent claims 6-8 and 29 indefinite. This rejection can be obviated by amending the claims to the amino acid sequence of SEQ ID NO: 5.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Drawn as enablement:

Claims 1, 6, 8, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factor to be considered in determining whether undue experimentation is required, are summarized in EX parte Forman, 230 USPQ (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims are drawn to an antibody-conjugated enzyme comprising modified dCK, the amino acid sequence identified as SEQ ID NO: 5 or any of its fragment as small as two amino acids (reciting as an amino acid sequence in claim 1) conjugated to any antibody comprising HuM195 recognizing CD33 expressed on the leukemia blast cells.

The specification on page 11-13 teaches that modified dCK (SEQ ID NO: 5) having increased kinase activity of original dCK to phosphorylate nucleoside analog, such as AraC, to increase the efficacy of the analogs. AraC, as a nucleoside analog prodrug, is a most active agent in treating acute myeloid leukemia. The specification also teaches that Arac is administered to a patient with antibody-enzyme conjugate that increases the concentration of nucleoside analogue NA-triphosphate in the targeted cell resulting in increased cytotoxicity in the cells. Although the specification particularly teaches that the conjugate of dCK and antibody to CD33, HuM195, recognizes the antigen on the tumor cell and is internalized into the cell, the specification does not teach whether or how the dCK conjugate penetrates the membrane into the nucleus to phosphorylate the nucleoside analog and kill the tumor cells because the process seems occur inside the nucleus, not in the cytoplasm of the cells. The specification does not provide any teaching on whether a fragment (an amino acid sequence) of modified dCK having the same ability as the modified dCK to phosphorylate the nucleoside analog or AraC.

One cannot extrapolate the teachings of the specification to the claimed invention because determining the function of the claimed antibody-conjugated enzyme requires undue experimentation, especially given that the modified dCK in the antibody conjugate functions and is located inside the nucleus of cells. In order to phosphorylate the nucleoside analog to treat leukemia, the antibody

conjugate enzyme needs to cross the cell and then nucleus membrane to get into nucleus. It is known in the art that dCK, as a chemotherapy agent, phosphorylates nucleoside analogs incorporated into DNA and cause cell death. It is also known in the art that the cellular DNA is replicated in nucleus and in the mitochondria and nucleoside analogs may interfere with DNA replication in both these sub-cellular location as stated by Zhu et al., (JBC, vol 275, page 26727, 2000, abstract). The instant specification although provides a teaching on the antibody HuM195 recognizing antigens on the tumor cell and internalized into the cell, does not provide any guidance on where and how the antibody conjugated dCK phosphorylate the nucleoside. As understood by one skilled in the art that the DNA replication during the cells division mainly occurs in the nucleus, the specification does not provide any guidance on how the conjugated enzyme get into the nucleus to phosphorylate the nucleoside analog before being incorporated into DNA and kill the cells.

Due to the limited teachings of the specification on where the antibody conjugated enzyme is located and functions and due to the lack of guidance of the structure of claimed antibody-conjugated enzyme fragment (an amino acid sequence), one of skill in the art would be forced into an undue experimentation in order to practice the full claimed invention.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bagshawe et al., (US Patent, 6299876, 2001) teach an antibody- enzyme conjugate that is used to generate a cytotoxic drug for cancer therapy. Bagshawe et al., teach the enzyme in the conjugate could be for nucleoside synthesis and specifically inhibits the incorporation of nucleoside to the DNA in the tumor cells since the antibody in the conjugate could bind to the surface of tumor cells (column 14). Bagshawe et al., do not teach or suggest the antibody conjugated to modified dCK of SEQ ID NO: 5.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
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